end-points then one would have to ask.

DR. ADAMSON: To in part answer Wayne's question, I think the only way Phase II windows will impact upon the speed of drug development, if we are willing to put into Phase II windows drugs where we have no activity data or the classic Phase II activity data is inactive. Now the past decade we have been unwilling to do that.

But just doing Phase II windows, where we have activity data, all it is doing, in my opinion, is delaying the decision whether to move into Phase III. It is not impacting our decision to move into Phase III.

Which circumstances can you put an inactive agent in classic Phase II in upfront, and where you have no data into upfront, I think carries still the same ethical considerations, but as far as speeding drug development process, until we are willing to do that, I don't think the Phase II windows are going to speed the drug development process.

CHAIRMAN SANTANA: Peter, I will take note to your comment that it has delayed. How has it

delayed the process?

DR. ADAMSON: Perhaps I will temper that.

(Laughter.)

VPI fos we knew was active. Or let me take perhaps a more recent example. Topo cyclo we know is active, and we know we have to do a Phase III study of it to determine if it is going to impact. Waiting for Phase II window data -- and I think the reality is we probably didn't wait; we only have so many opportunities to do Phase III. So I perhaps should restate it and say, I don't think it has accelerated our ability to do Phase III trials. In many cases the reality is we only can do so many Phase III trials in pediatric oncology and what to do in the interim.

CHAIRMAN SANTANA: Yes, I agree with you; I don't think, based on the data that we have so far, that we could definitely say that it has accelerated the process, but I think we have to recognize that it also has not negatively impacted on it.

Okay, Malcom?

DR. SMITH: I have several points. Chuck

Coltman's question was, has it affected outcome? That is an easy question to ask, but a very hard question to answer because every Phase II window is different. If you amalgamate four or five or ten different trials, there may be no difference, but one trial there could have been a difference in outcome. So it is a very hard question to answer, and they are small numbers, small differences that may or may not be significant, just because we don't have the numbers. So it is quite hard to answer that question with any confidence. We can't say they do or they don't.

The other point that you brought up is the question of parameters such as disease progression, and that is one thing that we can say with some confidence, is that disease progression is more likely in the single-agent Phase II window setting than it is when therapy has begun with conventional multi-agent therapy that we know is able to induce remissions or responses in neuroblastoma or Ewing sarcoma or osteosarcoma. So that's come from several different trials.

A third point, and one that I thank Steve

for circulating our commentary on the Phase II windows, but a point we made in that was that at first relapse many of these issues are the ethical concerns are reduced. The effectiveness of salvage therapy is diminished compared to the effectiveness of upfront therapy. Parents know about cancer treatment and are better able to assess whether they want to participate.

And Eric's point, these are tumors that have come back in spite of our known effective therapies, and presumably they are enriched for the clones that we most want to kill and we most want to identify active agents.

So I think in terms of looking to the future, and perhaps accelerating pediatric drug development, making better use of that, the first relapse, and looking at some of the new agents in that setting, potentially in a Phase II window setting, before proceeding to a more conventional salvage therapy has a number of advantages.

CHAIRMAN SANTANA: I will take one more question because I want to make sure we stay on time.

So we will let Dr. Cohn comment.

DR. COHN: Thank you. I just wanted to make one comment about the biologicals, and that is many of them I don't think would, even if we are ending up now deciding the Phase II upfront windows would not be a good thing to do, I think Pat's study, where he used retinoic acid, demonstrated very nicely that many of these biological agents work best in a setting of minimal residual disease. So to use them upfront, when you've got disease from head to toe, probably isn't the best way to approach some of these biologic agents anyway.

CHAIRMAN SANTANA: Susan, one last comment or question?

DR. WEINER: Yes, I had the dubious privilege of being involved in that consensus panel, as you describe it, a number of years ago. It comes as no surprise that the parents at St. Jude, with the kind of consent form that we had recommended, are not agreeing to participate in window trials for new patients, for newly-diagnosed patients. The parents' perspective is really give it the best shot you've

got, and a Phase II window trial is not exactly equivalent to that.

My question also extends to Drs. Smith and Hirschfeld, and that is that it was my understanding from this panel that this represented a set of guidelines by which to judge and decide on Phase II window trials in general. I wonder, what is the relationship was between these document and our discussion today and what guidance the FDA may take from that?

DR. HIRSCHFELD: We, I think, will defer that until after the break, when we have a very specific question which I think Dr. Santana will pose to the panel to help frame a response.

CHAIRMAN SANTANA: Well, with that, we will take a 10 -- Malcom, do you want to comment?

DR. SMITH: Well, just to address Susan's question in terms of, that guidance has really guided CTAP's review of Phase II window studies, and specifically in terms of the informed consents now do contain all of those things, and really the number of Phase II studies that have been initiated, single-

agent Phase II window studies has been small, quite limited, since the meeting. There have been some. They have conformed to the guidelines from the Phase II window meeting.

CHAIRMAN SANTANA: Yes, and at St. Jude, where we initiated some of these Phase II window trial concepts, I think we have been very, very attuned to following the guideline as much as possible. I think it reflects what you mention in terms of where we are with the informed consent process for these studies.

With that, I want to take a 10-minute break and resume half after the hour, so people can relieve themselves, and then we will get started and do the questions.

(Whereupon, the foregoing matter went off the record at 3:18 p.m. and went back on the record at 3:32 p.m.)

CHAIRMAN SANTANA: Okay, let's go ahead and get started, so we can finally get to some advice to the FDA on the questions that they have posed. They have posed four questions for us.

For the public record, what I will do is

I will read the brief introduction to the question, pose the question, and then we have asked Dr. Adamson and Dr. Rackoff to comment. The way we will do it is Dr. Adamson is going to take each one of the questions and give his perspective. We will have a public discussion about the question. We will move on to two, to three, to four, and then Dr. Rackoff will come at the end and give us an overview and his comments. Okay?

So the first item is the paragraph that's introductory to the questions that relates that, "The common approach for selecting starting dose for Phase I studies in children with cancer in cytotoxics is to begin at 80 percent of the adult maximally-tolerated dose, the MTD.

"Children who currently enter Phase I studies tend to be more heavily pre-treated with other therapies than historically had occurred. In addition, many newer therapies are not cytotoxic in the manner that previously-developed therapies were or may have different modes of action, including modulation of cellular-signaling pathways."

So the first question is: "If a potential therapy has an established dose in adults based on the optimal biologically-effective dose, the OBD, what principles should be applied to designing studies in children? For example, should the starting dose be a percentage of the adult dose, as historically has been done? Should the same exposure or AUC be targeted? And what role should pre-clinical data play in these kinds of study designs?"

Peter?

DR. ADAMSON: I will preface this by saying I tried to take the questions that Steve had originally posed and foresee what some of the comments might be. As you will see from these slides, I have been more successful on certain occasions and less on others. But it, I think, will serve as a bridging point for discussion.

So here are my way of restating the first questions. The first one that we are going to talk about is the Phase I design issues, optimal biologic dose, and then we will get to the following three. I will sum up and then turn it over to Wayne, talking

about the importance that we face in prioritizing agents, and then ultimately when should the rule be invoked.

So the first question, Phase I design, when one has the optimum biologic dose, how is this going to impact pediatric Phase I design? I think the challenge that we are going to face, if we try to implement this, is one of tissue acquisition. Frank Balis had commented on this earlier.

Essentially, the procedure must be minimal risk to be acceptable. So for leukemia studies, getting the leukemic blasts I think was going to be pretty straightforward; tumors invading the bone marrow, again, pretty straightforward. When we start moving beyond that for soft tissue tumors, immediately we are going to get into a more difficult area in order to obtain tissue. Ultimately, we will still be left with a question, as Eric posed, of: Are we really measuring the correct end-point? Not only is it important to know, are we measuring the correct end-point, but what is the specificity of the drug?

We have learned more often than not that

a drug we think is working in one way turns out to have worked in additional ways. So the mere fact that we are measuring one end-point, it may not be the most meaningful end-point to explain the biologic effect of the drug. In many respects, the fluorouracil inhibitors are a good example of that, where they have activity beyond mutated RAS.

I foresee that we are going to be using pharmacologic data as a surrogate more often than not, and in this case the AUC. The advantage of this is that by targeting exposure, it is really independent of what the specificity of the drug is for the target. In some respects it may be independent of what the mechanism of action is. If we have an exposure that is correlated with an effect, the challenges become and the dangers become, we don't always or we rarely know what the correlation between the plasma concentrations that we measure is with the target tissue exposure. Ultimately, we assume that there is some correlation, and it remains undefined. The hope, in fact, is that AUC turns out to be a good surrogate for tissue exposure.

How might this impact starting dose? I think even if we were fortunate enough to have data on what the optimum biologic dose truly was in adults, it may differ between adult and pediatric tumors. So the optimum biologic dose may not be the same in a pediatric tumor as in an adult tumor. Ultimately, what this means is we are going to need pre-clinical data at least to give us a relative comparison of what an optimum biologic concentration may be. If not an absolute, we may be able, if we use similar models, to say, for this tumor, we are going to need twice the exposure that we do for an adult tumor. Absolute exposures probably carry more dangers with them, but relative exposures may be a reasonable way to go.

Again, to emphasize that chances are the optimum biologic dose may not be known following adult Phase I or Phase II trials. Right now we are faced with, well, how long do we wait to have this data? If we truly wait until the adults are confident they have defied an optimum biologic dose, we are simply going to increase the lag time to initiate pediatric clinical trials.

So I think, although we need to look to the future, to a time when we can rapidly define an optimum biologic dose, over the upcoming years it may be premature to think that we are going to be able to do this. To delay pediatric trials excessively in an effort to define this in adults, I think is going to be doing children a disservice and is going to be setting pediatric drug development back further.

Finally, to come to pharmacology, and here I just want to build on what Mary and Clint and Steve have presented, but I want to take this emphasis: Phenotype matters. There is no question that pharmacogenomics, pharmacogenetics are critical pieces of information, but in fact, as Mary pointed out, genotyping is simply going to get easier.

What is not easy is defining phenotypes. In this case, phenotype, Clinton very nicely displayed some of the strategies where we can obtain phenotyping data with limited sampling methods, and I think we are going to have to look to do that more frequently.

Certainly, in Phase I trials we routinely define phenotype, and I think Mary gave compelling

reasons why we must start looking at obtaining genotype, because this is going to be the one clear situation where we are going to have both phenotype and genotype data available.

More importantly, I think, the Phase I pharmacokinetic/pharmacodynamic data that we generate will set the stage for Phase II and III clinical investigations, and I think there is going to be an ongoing need to obtain genotyping data and then phenotyping likely through limited sampling methods, not only in Phase I, but in Phase II and III.

So that's my few cents on question one, and maybe I will turn it back to Victor then.

CHAIRMAN SANTANA: Okay, further comments and discussion on question one? Dr. Bernstein?

DR. BERNSTEIN: I would just like to support Peter's point that really we don't want to wait until an optimum biologic dose has been defined in adults in order to initiate pediatric trials. We really want to get in sooner, and, in fact, as Eric was explaining before or suggesting before, that perhaps the place for us to get in is as early as the

dose level at which Grade 2 toxicities are being seen in adults, because at that point we know that there is at least a dose that has biological activity, and maybe we can think about initiating pediatric trials at that point, without even waiting for completion of the adult Phase I trial, and build into our study designs the fact that, if the adults are able to escalate very rapidly, that we can then skip a few dose levels in order to catch up, so that we don't have to duplicate things that have already been done.

So I would just like to suggest that what we want to do is work on study designs that enable us to get trials going sooner, to get trials completed in a reasonably short time, rater than waiting for as much information as we would need in order to define what is truly a biologically-active dose.

CHAIRMAN SANTANA: Clinton?

DR. STEWART: Peter, I heard you describe the optimal biological dose, and earlier I guess it was Ed talked about the biologically-effective dose. Frank talked about a minimally-effective concentration. Peter, you talked about measuring AUC.

We've got all these parameters floating around.

It seems like, I don't know, maybe that reflects sort of the confusion in the system. It seems to me if we were to pick -- this whole dependence on dose is a little bit concerning to me, and it goes back to the slide that I showed during my talk about the study that we did, the POG 92-75 study, where you escalate dose, but you are not escalating exposure. So you can change the dose until the cows come home, but you are not changing the exposure that the child is getting.

So I think we've got to be careful about this dependence upon changing dose and thinking that you are changing what kind of exposure that the child is getting. So I like the idea of the AUC or the minimum effective concentration that Frank talked about, but if we are going to do that, then we are going to have make the commitment of resources and the infrastructure to be able to follow through with that. It also means that I don't think we can do that with every agent that comes down the pike. I think we are going to have to be selective about that, because it

does require a great deal of work and commitment of resources to be able to follow through with that. So that's a comment.

The question I would ask you, Peter, this is a slightly different one, but you were talking about genotyping in Phase II and Phase III studies. Assuming that a patient is a genotyped in a Phase I study, you wouldn't genotype them again, would you?

DR. ADAMSON: No.

DR. STEWART: You are not talking about rephenotyping or regenotyping?

DR. ADAMSON: No.

DR. STEWART: Okay, I just wanted to make sure about that.

CHAIRMAN SANTANA: But let me follow up on Clinton's comment. I think the advice that I would propose, and certainly this is my opinion and certainly not that of the Committee, is that you have different scenarios. You have a scenario where there is a classical way of doing Phase I studies, where you start at some level that has either been predefined based on adult data or concomitantly as the adult data

and the pediatric study are being done.

I think that will apply and has worked very well for the majority of the things that we have done with cytotoxics. Continuing with the cytotoxic story, but there may be certain drugs, which Clinton was referring to, in which we may have pre-clinical data that supports that a different concept be applied to defining the escalations or how the Phase I study is done. I can't give you a broad recommendation on that. It is going to depend on what pre-clinical data exists, either from relevant pediatric models or other models that may exist that would then indicate that maybe a different end-point, like the AUC or the systemic exposure, may be more relevant in applying your design to the Phase I concept.

So I think for cytotoxics we want to move to No. 2, but we have to recognize that there is not a lot of infrastructure to support that at present, and that we have to be very selective in which drugs we could apply that principle to. Although ideally it should be with every drug, I don't think realistically we are at that point yet.

For biologics, I think it is a completely different story, in my view. I think the principles of the traditional Phase I escalation I think may not, as you heard earlier today, may not apply. I think in those settings I would argue more like Frank was saying earlier, that in those settings with biologics, not cytotoxics, that we do the parallel scenario studies, because, clearly, the differences in activity or potential toxicity may be very different in the populations.

DR. HIRSCHFELD: May I just ask for a little clarification? I thought I was hearing that it might be appropriate in the Phase I study to look at, as an end-point, the first doses which you see Grade 2 toxicity, independent of whether there is a target or some other biological assay, but that your Phase I study would guide you toward a toxicity, and that, in turn, would be informative.

CHAIRMAN SANTANA: Do you want to address that? I think you were the one --

DR. ADAMSON: I didn't raise it, but, Ed, if you want, I think the intent is, when you see a

Grade 2 in adults, is that a reasonable time to say, okay, this is a reasonable dose to start in children, and then we can catch up to wherever the adults are when they have gotten to their MTD or closer to the MTD? At least that was my interpretation.

DR. KORN: Yes, I just want to add, I mean, I didn't say it, but it should be understood, of course, that if you are using a molecular target or some targeted response, that if you see toxicity, you have to stop escalating and back off.

DR. HIRSCHFELD: Thank you for that clarification. Just so that we understand, a potential direction for Phase I, an adult study would have as one of its end-points some toxicity, independent of whether a targeted dose or some bioassay was going to be invoked, and that that toxicity, in turn, could be a guide for initiating pediatric studies.

CHAIRMAN SANTANA: Malcom?

DR. SMITH: Two comments: One is that, in terms of the AUC and that as an end-point, you know, we have done that with 06-benzyl bromine, and so

there's precedence for doing that, and I agree completely with Peter that I think we will be doing that more and more in the future as we have a systemic exposure that has the appropriate effect in adult patients, and then we want to make sure that, when we use a similar dose in children, that we are attaining that systemic exposure. So we have done that, and I think, as Peter says, we will be doing that more in the future.

The second comment is I would caution, we can do what Steve just asked and what Ed said; we can start at the first Grade 2 toxicity. I would caution our goal isn't to start pediatric studies as quickly as we can. Our goal is to complete them as quickly as we can. If we add five or ten patients below the MTD, using that design, whereas using another design we add all of the patients closer to the MTD, and that takes your patients, then, in fact, we are studying more drugs; we're completing perhaps more studies more quickly, and the point I made earlier: that because adult Phase I trials can be completed so quickly with dose levels occurring very quickly, the rate-limiting

step with the design that Ed described is most commonly getting to the adult MTD, so that you can jump over three or four levels in the pediatric study to get to that.

So I think we need to keep our eyes on the prize, and in terms of Phase I that is the number of drugs that we can study, hopefully, picking the very best ones that we can.

DR. ADAMSON: Yes, I agree, Malcom, to an extent. Part of the problem, at least over the past few years, has been that we haven't had enough drugs to study for children, and that we have had children who simply have not gone on to study because there were no open studies.

So it is always a balance as far as -- it is not only completing studies on time, but it is making studies available in a timely fashion. I don't think there is a hard-and-fast rule as far as when to start. Clearly, for some of these, we have started, in my opinion, much too late, and that is when the drugs have been on the market.

But there will have to be a balance to

when we think it is appropriate, and certainly, if all patients are going on to open studies where the adult MTD is known, then there will be less pressure to open studies earlier.

DR. PRZEPIORKA: During lunchtime I was encouraged to re-ask two questions that were deferred from this morning, one of which had to do with the dose when moving from an adult to a pediatric study, and whether or not you should continue on a milligram-per-kilogram dosing versus milligram-per-meter-squared, especially in light of the fact that we recently have a drug that went out with a milligram dosing in adults without any basis on weight whatsoever? So no one is sure how to do this in children.

Secondly, just to readdress the question of what is clinical and what is research, and we have now the option for participants not to participate in the pharmacokinetic studies. How many patients do you really want to get pharmacokinetic studies in this heterogeneous pediatric population before you're certain that you really have the dose to get the right

AUC?

CHAIRMAN SANTANA: Clinton?

DR. STEWART: Well, I would actually like to address the second question first, and that would leave Steve with the first question, which is the more difficult one.

The issue of clinical versus research, as far as it goes with pharmacokinetic studies, I think is a very important one and actually one we talked about at lunch today. A Phase I study, let's talk about that specifically first. Whether it is part of the primary objective or part of a secondary objective is one way that we look at it at St. Jude, whether or not is considered in the informed consent aspect, is whether or not a child is to be -- to participate in the study, to receive the study drug, that they have to participate with the pharmacokinetic studies. If it is a secondary objective, it is part of a checkbox and they are allowed not to participate. I guess that is just one comment.

CHAIRMAN SANTANA: Could I follow up on that, Clinton?

DR. STEWART: Yes.

CHAIRMAN SANTANA: I think the point is that if the end-point is that you are going to define the toxicity based on a pharmacokinetic parameter, you can only realize that end-point if you get PK; whereas, if PK is a secondary issue to the design, that the main design is a completely different question, then I think in those circumstances then the option of yes or no PK is something that you can allow.

DR. STEWART: Right.

CHAIRMAN SANTANA: But in the first scenario, if you are really trying to define the toxicity based on AUC, how can you not get PK? In that scenario it is absolutely crucial to that study. So you either participate in the study or you don't.

DR. STEWART: Right. So then the second part of your question is, how many patients do you need? And that is something that I have been listening to as we talk about the number of patients in a Phase I study. I mean, obviously, one of the things you want to do is to minimize the number of

patients that receive what is considered -- and I hesitate to use this term, but a subtherapeutic dose and maximize the opportunity that a child would have for a therapeutic response.

So you want to try to minimize the numbers of patients in a Phase I study, I would assume, and yet I counterbalance that with the need to learn about the disposition of a drug in the pediatric population. One of the references that Steve sent out was the paper from Elizabeth Eisenhower, who was an author on it out of JCO. It was a consensus conference about Phase I studies. My colleague, Mark Ritane, wrote in that about the need for studying additional patients, and one of the ways he suggested doing it was to study more patients at the MTD. So you had 20 to 30 patients -- this is in the adult population -- 20 to 30 patients at the MTD.

Now Dr. Boyett is over there squirming in his seat because, you know, there is no way to say that is going to provide a, quote/unquote, "statistically-valid" estimate of clearance in that particular populations, but what it will do is it will

give us a better handle on the estimates of clearance than studying two or three children at a particular dose.

So how many children do you need? I can't give you that number, but I can tell you we do need to study an adequate number of children, more than, say, six or eight or ten. I would be an advocate of being sure that in our Phase I studies we don't sacrifice the knowledge that we need to gain from those pharmacokinetic studies that we can use as we move into the Phase II, that we just don't sacrifice that knowledge.

CHAIRMAN SANTANA: Dr. Bernstein?

DR. BERNSTEIN: I won't disagree with Clinton about the pharmacokinetics, but I would only disagree with the setting and say that what we can start to do more of is, as we take drugs into Phase II, especially if there is a limited sampling strategy that has been designed, is that we can look at the pharmacokinetics in the initial Phase II population as well to complete the number that is required to actually get an idea of the things like Clinton is

talking about.

CHAIRMAN SANTANA: Have we satisfied this question, Dr. Hirschfeld?

DR. HIRSCHFELD: I think Dr. Leeder was going to make a comment --

CHAIRMAN SANTANA: Oh, I'm sorry.

DR. HIRSCHFELD: -- about dosing, yes.

DR. LEEDER: Well, these discussions have been recorded for all posterity, and I really don't want to go down on record as the individual who sets policy for converting adult doses to pediatric doses. But there are a couple of points worth making.

One point is that, until November the 19th, which is when I got the email message from Steve that kind of laid out what might be expected of me, and this is specifically this issue of converting adult doses to pediatric doses, I had not really seriously considered this whole aspect of the ramifications of correcting clearance for body weight versus body surface area versus liver mass, or whatever it is.

It is my impression only, without having

a detailed slog through the literature, that the apparent differences in clearance between adults and pre-pubertal children tend to be less when corrected for body surface area than for kilogram body weight. Now I don't want to completely cop out on an answer, and what I am going to suggest is that perhaps some of the information is available to us, and some of the notes that I made have been to go back and look at some of the existing pediatric data for compounds such as medazalam, carbomezapine, which are pretty well accepted to be measures of P450A4 activity, for example, where there are a lot of pharmacokinetic data in children.

I think one thing that needs to be borne in mind is that pharmacokinetics classically have described the disappearance of the parent compound. In cases like Irinotecan, where it is an active metabolite, what is important is probably the exposure to the parent compound. And the point I am trying to get at is the fact that perhaps the pediatric clinical oncology arena maybe ought to take advantage of some of the information that is available for some

compounds in the pre-clinical testing phases with respect to in vitro drug metabolism.

Certainly for a lot of compounds there is a process that is called reaction phenotyping, where a battery of human liver microsomes that have been phenotyped for particular activities, recombinant heterologously expressed human enzymes, are used to map the drug metabolism pathways that are involved in the disappearance of the parent compound, and perhaps the formation of the pharmacologically-active anti-neoplastic compound, with the intent of at least identifying polymorphic pathways or perhaps some would say avoiding them. Maybe you don't want a compound that is a substrate for 2D6 which is deficient in 5 to 1 percent of the Caucasian population.

The other reason this process is completed is to characterize and perhaps minimize drug-drug interactions. The point I am trying to make is that, if we go back through the literature and look at this issue of clearance with respect to the metabolic pathways, the specific metabolic pathways that are involved, how those metabolic pathways change during

development, whether or not they are better correlated to thing such as a correction for body weight, body surface area, or liver mass, that it may be possible for specific compounds to put all this information together and come up with some sort of a rational conversion factor.

But, as a starting point, again, I would like to repeat that my impression is that the differences are probably least or less with body surface area than with kilogram or total body mass, and I think it is just a little bit premature to pursue the liver mass at this point in time, until we do a few more studies.

CHAIRMAN SANTANA: But how do we address the issue that Donna was trying to, I think, hint at, which is, we have a product or an agent that's been approved on a milligram basis? How do we really relate that in terms of the type of studies and where we start in pediatrics? Because to me that's an issue. Can you shed some light on that? Because I think we are going to be seeing that more and more with some of these biologics. It is not going to be

milligram per kilo, milligram-per-square-meter. It is going to be some total dose.

DR. LEEDER: I find, and maybe Clinton can comment on this as well, I find it very difficult, just from the concept of dumping a specific mass of drug into a volume of varying ranges, to be able to predict what concentration is going to come out. So I would probably pick any correction over a straight milligram dose.

(Laughter.)

CHAIRMAN SANTANA: Clinton?

DR. STEWART: So, as you probably know, we are faced with that with one of the upcoming clinical trials that we are going to have. One of the things that I have proposed, and Peter and I have talked about this, is then the first three to five patients, what we will do is we've got the dose; the dose was decided in adults in milligrams. We have converted it using a 1.73-meter-squared typical adult to a meter-squared, milligram-per-meter-squared dose in children. So what we will do is we've got the assay up online, and the first three to five patients we'll measure the

concentrations and we will see what the levels are in our children relative to what they were in the adults, and we will be prepared to go from there.

So, I mean, that doesn't help the first child that is enrolled in the study very much, but that is how we are going to be prepared to react to that situation. So, I mean, that is one thing I can offer up.

One other thing I would like to say in terms of our experience with Topotecan, and I tried to allude to it a little bit earlier with the infants, the children less than two, it does appear that, if one were to normalize the clearance for body weight per kilogram, it does seem to normalize the differences between the infants and the older children.

So what I am saying there is I think that we have to be very careful when we talk about children. All children are not the same. You've got the little children, and then you've got the bigger children. I think that, as Steve pointed out, there are maturational differences in the way that they

eliminate drugs. So we've got to be careful about just making the straight -- I mean, it is a difficult conversion from adults to children, but then even within the children, quote/unquote, "children" population, we've got infants and then those kinds of considerations. So I hate to make things even more complex, but we have to consider that.

CHAIRMAN SANTANA: Steve?

DR. LEEDER: If I could make one comment that might help simplify things, again, it goes back to this point that the closer the children -- for example, adolescence, post-puberty, chances are when you look at -- let me back up a bit and say maybe we can get some insights, for example, from the shapes of growth curves -- we all have access to the growth charts -- and look at when the growth charts start to flatten out as being the points where there are fewer changes with age.

So one of the areas where the growth charts flatten out is after puberty. So perhaps it might be possible to go directly from an adult dose, using an adult dose on -- correcting for whatever

index you wish -- in a post-pubertal individual.

Before that point, it gets a little bit more difficult. Certainly the most difficult region would probably be the first year of life, I think where it is such a dynamic process that I would hate to predict what the appropriate scale ought to be in converting an adult dose to an effective but not toxic, or an optimum, dose in that age range.

CHAIRMAN SANTANA: Pat?

DR. REYNOLDS: I think one of the things we haven't considered in this is that you have very young children. You can't often take the formulations that are developed for adults. We certainly see this with the oral retinoids as being problem.

So the bioavailability of these agents, if you are dumping it out of the capsule and trying to mix it in with applesauce, or whatever it is, is going to change. So that is another parameter that needs to be considered in this. You can't necessarily directly translate these formulations, and some formulation development may be necessary.

CHAIRMAN SANTANA: Okay, I think we have

pretty much covered this, Dr. Hirschfeld, unless you wish for us to make any comments?

DR. HIRSCHFELD: I thank you for all the input.

Did you have something you wanted to add, Dr. Rackoff?

DR. RACKOFF: Pat made the point I was going to bring up.

DR. HIRSCHFELD: Okay, excellent. Okay, let's move on then.

CHAIRMAN SANTANA: Yes. So the second question has to do with, and I will read the question, but it has to do with issues of extrapolation and then what efficacy data would be necessary for product labeling for pediatric indications. So the question reads, for the record:

"If tumors that are considered to represent the same disease or condition are found in two different populations and/or share a common biological mechanism that is supported by a body of scientific evidence that is generally accepted, and a therapy targets that mechanism, what type of studies

would validate extrapolation of efficacy findings from one population to the other?" So this is the question of extrapolation of data.

Then the second part to the question is: "Product labeling to support a marketing claim usually is dependent upon demonstration of a patient benefit and an assessment that it is safe and effective for the intended use. If activity is noted in adults, and the same tumor type, based on generally-accepted criteria, such as histology, cytogenetics, common biological mechanisms, et cetera, exist in children, what evidence would be needed to establish efficacy for product labeling; that is, to make a market claim for children with cancer?"

Peter?

DR. ADAMSON: I have very little to put forth, but I will throw out a suggestion. I think efficacy extrapolations are going to only apply in limited situations, for all the reasons you have simply stated in that question, where biology, and so forth, is the same between adults and children.

However, we all can name situations where

that occurs. In my opinion, we are still going to need Phase I, and likely some Phase II data, in pediatric patients. However, if the pediatric Phase II data is consistent with the adult Phase II data, I would argue that that ought to be sufficient to extend labeling, if the adult randomized trial has shown efficacy, and that we need not attempt to repeat, nor would we likely have the ability to repeat, a Phase III randomized trial in children.

My only other comment along these lines comes back to, Steve, one of your opening comments about when the rule would be invoked. If I understood correctly, you said for certain diseases, an automatic waiver would be granted: prostate cancer, breast, lung. I would argue that granting an automatic waiver for that would be detrimental to pediatric patients.

The reason I say that is that one can envision that there is a new agent, a signal transduction inhibitor that's highly effective in prostate, and that signal transduction pathway we learn is a relevant pathway for pediatric tumor. If a waiver is granted, then we will be doomed in that

situation.

So maybe I will leave it there and let the discussion follow.

DR. HIRSCHFELD: Well, Peter, first, I want to thank you for the advice, and I think the advice you propose there is at least consistent with our thinking on the question.

In terms of, we'll take the prostate cancer paradigm. If one is defining the indication, and this would represent a paradigm shift, if one defines the indication as, we'll say, a certain Gleason stage prostate cancer or hormone refractory prostate cancer, that's one circumstance. But if one is defining the indication as tumors that are dependent on a certain signaling pathway and have other characteristics, then the Pediatric Rule could be invoked.

When the rule was first developed, we didn't have, or didn't anticipate, the tools to make these, what could be called, cross-histologic diagnoses or mechanistic-based. But our thinking has evolved as the science has advanced, and what we would

need would be a very firm scientific basis to make that extension, but if there was a firm scientific basis to make that extension, then in that case I think the rule could be triggered.

I would like to ask Dr. Pazdur if he would add some comments?

DR. PAZDUR: What you want and what we may want has to be supported by the law, because basically this is a mandate. Okay? So it is not an optional thing or it's not like, "Would you please study this perhaps?" It is a requirement that the companies study this, study the indication.

So, as Steve mentioned, it would have to be kind of a paradigm, king of sea change, where the academic community, treating oncologists in general, and a general scientific acceptance would be that these are the same diseases or entities that would represent identical populations with the same disease.

It couldn't be just that we're studying a drug that has overexpression or targets topoisomerase 1 and, therefore, we are going to then make the company study all tumors that have overexpression of

topoisomerase 1, do studies in pediatric tumors, so express that.

So it is really a level, since this is a requirement and a mandate, that has a legal implication that we would have to be very careful in applying and would have to have a scientific foundation that is well-accepted by the community.

CHAIRMAN SANTANA: Just as a followup of that in terms of my own perspective is I think in terms of these issues of two populations and what data can be extrapolated from one or another, and although the question is posed as an efficacy question, I would caution that safety also has to be a part of the equation. So when one tries to extrapolate data from one population to the other, one has to look at certain parameters that may indicate a different scenario of safety may be similar to some of the PK discussions we've had earlier today.

So it is just not a matter of saying the populations are very similar in terms of the diseases, in terms of the biology, and therefore, the efficacy should be the same, but there may be some minor

differences in safety that also should be a part of the equation.

DR. HIRSCHFELD: I appreciate that comment, Dr. Santana, and that is a major concern not just in oncology, but across all of pediatric therapeutic development in terms of, how do we know that we are getting adequate safety data, that something could be labeled?

Just, Peter, one other point: We have another program, an incentive program, for those circumstances where we would like to encourage development in pediatrics but we can't invoke a mandate. That program has been spectacularly successful in general. In oncology we have found that companies are now learning about it and have not been shy about making proposals.

CHAIRMAN SANTANA: I want to also make a comment regarding the second issue, which is that, once you have established this commonality in terms of the disease and the biology, then what additional information would you want to legally support a product claim for children with cancer? My position

would be that, if the agent that you are discussing, that you are targeting, is a biologic with the common pathway, and that indication exists also in children, that you would have the same requirement, that you would require a Phase III study that would indicate the impact of that, wouldn't you?

DR. HIRSCHFELD: Not necessarily. We have been exploring broadly in pediatrics the issue of extrapolating efficacy findings. I think the paradigm that Dr. Adamson was discussing is something which might be acceptable. I don't think there would be a regulatory requirement to repeat an efficacy study with the definition -- and I'm looking at our colleagues over in that corner -- that an efficacy study is a study which is designed to establish the efficacy rather than just demonstrate an exposure/response relationship. I think the exposure/response relationship could be sufficient, but I will ask Dr. Pazdur.

DR. PAZDUR: Yes, I think I would agree with Steve. Let's take a specific example. If we were dealing with Hodgkin's Disease and somebody did

a randomized study and proved the efficacy and combination of a drug and proved what we would be looking for, probably a survival advantage or a curability clinical benefit, probably since the disease would be quite similar in a child, the childhood population -- and correct me if I am wrong since I am not a pediatric pediatrician -- but if that was a similar disease, we probably would accept Phase II data, since it probably would be very difficult to do and replicate a Phase III trial in that identical population.

Here, again, it really depends on how comfortable we are that these are exactly the same diseases, but we don't want to be overregulatory or overburdensome in this regard. I think there could be a kind of bridging that could occur with Phase II data here, again, emphasizing the safety that you previously mentioned for a pediatric population and look at a surrogate end-point such as response rate toward a particular disease, and making sure the duration of that response was meaningful.

CHAIRMAN SANTANA: Thanks for a

clarification.

Other comments or questions? Jerry?

DR. FINKLESTEIN: This question is either to Rich or to Steve. At the last meeting we spent a lot of time in comparing adult and pediatric tumors. In fact, we made the comment maybe histology was on the way up because molecular biology was on the way in.

My question is whether the incentive program would apply to those pharmaceutical companies that would like to use molecular biology as a way of studying pediatric tumors. Using your example of prostate cancer, for example, with some signal, could that be invoked and would you accept that? So I am asking it, actually, from an industrial point of view.

DR. HIRSCHFELD: The incentive program doesn't require any relationship between the adult tumor and a pediatric disease. In fact, within the FDA in general we have adult indications which were approved in one Division, in one disease area, and the pediatric indication that is being studied is in a completely different area. So there's no need for a

biological or mechanistic linkage in any way.

However, if the rule is invoked, that does not preclude qualifying for the exclusivity extension. That would then require further discussion. It is not an automatic trigger or something that one can assume. It would require specific discussion, but that's plausible.

DR. PAZDUR: I think it is also important to put in context the rule as it can be applied. What we are dealing here, from our previous meetings, is a relatively limited number of diseases that really go back and forth. You could talk about acute leukemias, for example, some lymphomas, some brain tumors.

But, remember, the sponsor has to be studying the drug in that indication in the adult population, and really when you take a look at what indications are being studied in adult populations, for example, they are the big diseases. They are breast cancer. They are colon cancer, prostate cancer, pancreatic cancer. We have very few applications where the rule really can be nailed down, where we could have this linkage between and exert our

regulatory authority in that regard. So I think we have to put this in some context of the real world, and that is why, as Steve already mentioned, the exclusivity arrangements probably have a greater degree of flexibility really to encourage drug development in pediatrics.

CHAIRMAN SANTANA: Dr. Boyett?

DR. BOYETT: Just a point of clarification: Suppose you take your Hodgkin's Disease example and you've got efficacy data in adult and you do a Phase II trial and you show some response in pediatric Hodgkin's Disease. So now you grant a labeling indication in pediatrics.

You know, there are very few pediatric cancers that are cured by single agents. How to incorporate one of those single agents into a regimen, that's a different question. If you grant this labeling, what is going to be the implication of COG, for instance, trying to learn how to use this particular drug in a regimen to treat newly-diagnosed Hodgkin's Disease patients?

DR. HIRSCHFELD: Our history of approvals

is actually that very often in the label the product that is being granted the claim is being granted the claim as part of a regimen. A recent example is the approval of Irinotecan, where it isn't Irinotecan that is approved; it is Irinotecan in the use with combination with other drugs in a particular setting.

So in the case where a new Hodgkin's therapy would come along, boy, if we had something that is as a single agent could treat the disease, that would be fairly spectacular, and it would warrant that. But, in general, the data that are being submitted are data where it is not for monotherapy but as part of what, hopefully, is a therapeutic advance over previous regimens.

Rick, do you want to comment?

DR. PAZDUR: Yes, because probably what we would do in the adult indication, it probably would be used in combination with other drugs, and that same combination would be studied in the pediatric population, looking for similar response rates between the adult population and the pediatric population. Here, again, it is a bridging aspect. We wouldn't

just take a single agent and say, well, you have 20 percent response rate and, therefore, have activity in Hodgkin's Disease and say, well, that's sufficient for approval in --

DR. BOYETT: I guess I was misinterpreting the use of Phase II here because your intent in --

DR. PAZDUR: Let me clarify that.

DR. BOYETT: Yes.

DR. PAZDUR: Probably a more accurate description would be a single-arm trial looking for response rate.

DR. HIRSCHFELD: An exposure/response study is what we usually use in broader pediatric term, not Phase II in the narrow sense.

CHAIRMAN SANTANA: Dr. Korn, one last comment on this issue, please.

DR. KORN: Well, that's going to be kind of tough now, isn't it? So you're going to have a combination therapy, a small Phase II trial, and you are going to try to show that response rate, whatever, is consistent with the small Phase II adult study. I mean, I'm not sure what that means. You almost can

say, well, why bother, because you're not going to find anything out from doing that anyway?

DR. PAZDUR: Well, here, again, I think there is some elements of safety that we would consider by looking at it in a Phase II study, which I think is important, as Victor implicated. Remember, these diseases -- and here, again, the link of how comfortable we feel between the disease and the child and in the adult is one that is really going to mitigate what degree of information that we would want from the sponsor and the clinical trial. If we really believed that these were identical diseases, to make a sponsor do a separate Phase III study with a combination against the standard therapy of "X" hundreds of patients may not be warranted here to show either superiority or non-inferiority.

DR. KORN: Right. Well, the alternative is not to do the Phase II study, but do a small safety study then.

DR. PAZDUR: Here, again, the Hodgkin's disease might not be the best example. It is an example that I threw out, but, here again, a lot of

these factors are mitigated by how comfortable the feeling is and the scientific underpinning between extrapolations.

DR. HIRSCHFELD: I would just add to that that I think we're ethically bound to do the studies only in patients with the diagnosis. If we did even some modest study and saw no responses, I think everyone would begin to get worried. So although the purpose of the study wouldn't be to establish efficacy, you would certainly want to make note or want to be reassured that you were getting the same type of response.

DR. KORN: Right, but I can understand for mono-therapy but for combination therapy, you are going to get responses. So that's not going to really be an issue.

CHAIRMAN SANTANA: That would be the added value.

Okay, let's move on because I think we have covered this one pretty much.

So the third question is relevant to mono-therapy versus combination therapy. That is, "If a

therapy is intended to be used as part of a combination, are monotherapy studies in children advisable? If so, what types of studies should be implemented prior to initiating the combination studies?"

Peter?

DR. ADAMSON: I'll just comment. We are more limited in pediatrics than we are in adults in this situation. If a single agent has no prospect for direct benefit, and is greater than minimal risk, we cannot perform a single-agent study, I think. At least that would be my interpretation of the regulations.

However, I think -- and I kind of shudder to have used the word "window" here, but I think one can consider a single-agent window, and let me expand what I mean by that. Where one starts with a new agent, determines acute toxicity, defines some pharmacokinetics, and continues with a combination, and I have a couple of examples that I will share with you, which is where we have taken this approach.

The first is a study that Frank Balis and

Kathy Warren led with RMP-7 and carboplatin, and the subsequent one will be a study that COG will be starting soon with the antisense compound Genasense. So RMP-7 is a drug that modulates the blood/brain barrier. There was a fair amount of pre-clinical data and some adult data that it could potentially increase the efficacy of standard cytotoxic agents, but by itself RMP-7 was not known to have any anti-cancer potential.

So the pediatric trial design was the following: The first day of the first cycle of therapy, the patient received Cereport as a single agent to determine its acute toxicity, its acute tolerability, as well as the pharmacokinetics. Then it was immediately followed in day two and day three of the first cycle by the combination of carboplatin and Cereport, Cereport being administered at the time of peak carboplatin exposure.

All subsequent cycles were then two-day exposures of just the combination of the two. So in this case we know we were not getting data as far as any chronic toxicity of single-agent Cereport. This

is a drug, however, that essentially only has acute toxicities, but we were getting a fair amount of information at the same as allowing patients a full benefit in a given cycle of being exposed to an active combination.

Similarly with Genasense, which is a BCL2 antisense compound, the trial design that we are proposing, and that CTAP will soon review, is that there is a lot of data, first of all, that to get maximal decrease in BCL2 expression, you need a sustained exposure to the antisense compound. So there will be a seven-day continuous infusion study of the antisense compound, and during the initial four days the patient is only going to be exposed to the antisense compound as a single agent.

We will get some acute toxicity information here. We will get some pharmacokinetic data here, and then during that first cycle they will then get exposed to the combination of some standard cytotoxic agents, in this case doxyrubicin and cyclophosphamide, in conjunction with the agent that by itself would have minimal activity as a single

agent.

So we have addressed this in pediatrics, and we have done it in situations where it has been, I think, relatively straightforward to do, and that is when we are either anticipating only acute toxicities or when the biology of the drug action warrants administration of the drug prior to combination.

However, during a trial where there is just a cycle of drug with no potential for therapeutic benefit, I do not think it is going to be feasible in pediatric patients.

CHAIRMAN SANTANA: Yes, I want to expand on that. I think that the intent defines the study that you want. So if we know pre-clinically or from some other data that the agent by itself doesn't play a major role, I think it would be both scientifically and ethically invalid to do a single-agent trial if ultimately that is going to be needed to be done in combination.

So I think one has to be very specific about the agent that one is talking about, and what one knows about that agent a priori before one

mandates that that agent be studied as a single agent, based on the intent.

DR. PAZDUR: How does one know actually that, that the agent has no activity? You know, here again, there is activity and activity; one could be activity measured as response rate for a cytotoxic drug versus time-to-progression for a more cytostatic therapy, and just to say, well, because the drug does not produce response rate, one does not have to demonstrate single-agent activity would be somewhat hard necessarily to swallow for us.

CHAIRMAN SANTANA: No, I agree with you. I think with cytostatics, it is very controversial and it is very difficult. With cytotoxics, I think it is a little bit easier in terms of answering the question. With cytostatics, you are faced with the issue that you really may not know if by a single agent given over a prolonged period of time you do get some activity.

So I think in that scenario you are really going to have to rely very heavily on some pre-clinical data and what data you may discern from adult

studies before you mandate a single-agent pediatric study.

Frank?

DR. BALIS: The area this most applies to is modulating agents, agents that modulate resistance, for example, to anti-cancer agents, where giving them alone obviously makes no sense.

But the other, the converse is also true. There are a number of studies with MBR inhibitors in adults where the agent, the chemotherapy agent, was given alone, and then on a second cycle it was given with a modulating agent.

I think I have the same difficulty doing that type of trial in pediatrics, in that many of the diseases that we treat tend to progress very rapidly if not given effective therapy. So even doing a chemotherapy alone followed by a cycle later with modulating agents I think is a difficult trial design to undertake in our population, if there has been efficacy shown for that modulating agent in adults.

CHAIRMAN SANTANA: Any other comments or advice on this issue?

(No response.)

CHAIRMAN SANTANA: Okay, so let's move to the fourth question which is the Phase II window design. For the sake of time, I won't read the paragraph, but I think the question is: "What circumstances (for example, types of diseases, expected results with available therapy, prognosis, types of patients) would warrant a Phase II window design?" And I'll let Peter comment on that, and then I will give my insight, too.

DR. ADAMSON: I think I made my opinion known. So, in fact, I don't even have a slide on this one, but I would echo what Malcom had said earlier. I think in order to accelerate the drug development process, we need to start believing our own data. In the relapse setting for that vast majority of childhood cancer, not all but the vast majority, including high-risk ALL, we, in general, don't have meaningful salvage therapy coming off of current frontline protocol.

I think a Phase II window study that either a modulating agent or, in fact, a novel agent

in certain circumstances may be more appropriate in the relapse setting than it is going to be in the upfront setting for diseases where there is no known effective standard therapy, and I would probably limit that to brainstem glioma at this point. It may be acceptable to do it there. However, beyond that, I think we run into many of the ethical issues that have been discussed, as well as the value of doing them that I had mentioned earlier.

CHAIRMAN SANTANA: Yes, my comment was going to be, as you heard earlier, that I think the consensus document from four or five years ago has been a good tool and a good guideline for answering this question. Until that document is revisited, I think that document should serve the basis to answer this question.

So for those of you who haven't read it, I would encourage you to read it because I think it does provide some insight into the potential type of patients, the expected results, and some of the relevant issues regarding the ethics of these trials. So until we revisit that guideline and that consensus,

I think that serves as a good parameter for us to answer this question to give advice to the FDA.

Frank?

DR. BALIS: Yes, I think we are moving into targeted therapy. The one potential area where it could be useful is if we want to define a biological effect of a drug that has a specific target that is completely separate from any effect that standard therapy has on a tumor, because so many of our tumors now are treated neoajuvantly, and we have the opportunity potentially to get tumor tissue, because we are doing a clinically-indicated procedure in those patients at some point later during their therapy that we could administer drug maybe even in combination with standard therapy during the neoajuvant phase, where we could measure a biologic effect when we go in and actually remove their tumor.

DR. BERNSTEIN: I think that Peter is a little overly restrictive about disease categories. I think there are a variety of sarcomas, metastatic at diagnosis, for instance, where the prognosis is sufficiently poor so that one could consider the

addition of new agents early on rather than waiting for recurrence.

I won't push the point too hard because I actually think that, for the immediate question, which is, how are we going to give guidance to the FDA, I think that there will be rare circumstances in which window trials are actually going to be very informative in terms of the things that you're looking for.

I agree with what Victor said, that I think the document that was produced by our consensus meeting, which with Susan I had the privilege of attending several years ago, I think is reasonable as a guidance.

CHAIRMAN SANTANA: Do you want to make some final comments and then, Wayne, because I think we are running short on time?

DR. ADAMSON: Yes, I am going to turn this over to Wayne. The only one I want to talk about, and I am going to jump to that, is on prioritization.

The challenge for us is that we simply cannot study all the drugs that are in the

developmental pipeline in children. So we have a choice. We can do it randomly or we can look at pre-clinical models that we know in most cases have not yet been validated, but at least may give us some basis for helping to prioritize.

What I find is a remarkable situation now -- and, again, this may be a little bit overstated, but with FDAMA in the final rule, we are faced with a situation whereby it may be easier to administer a new drug to a child with cancer than it will be to administer the new drug to a mouse. I say that because intellectual property issues now -- and this is a two-way street; this is not just industry; this is academia working with industry, and basically lawyers going at it with lawyers -- where we have no pre-clinical data in pediatric tumors at a time when we are ready to embark on pediatric studies.

This is a situation that we are going to have to address, and we are going to have to improve upon because the problem is just going to expand as the number of agents in the pipeline increase. Until we solve the issue of overcoming the intellectual

property debate, where we can get new agents into models that we openly will say have not yet been validated, but which we intend to validate over time, we are going to be operating in the blind as far as being able to prioritize.

That is simply stated here, that I think pre-clinical models for pediatrics, we are likely to have to rely on more heavily than one will have to do it in the adult situation.

So let me turn it over to Wayne, who I think is --

DR. RACKOFF: In the interest of time, I will just do it from here because I've only got three or four slides, and I'll provide them, if you want, but they are fairly straightforward and really address the last two points.

I just want to warn people that the last Advisory Committee I took part in was in 1977, the National Health Insurance Advisory Committee. I was a staff member, and you know how successful that was. So I hope this project will be a little more successful in coming up with specific guidelines.

I am speaking now, it is not the opinion of Johnson & Johnson; it is not the opinion of any one group. Raj Malik and I, who chair the COG Committee, have conferred a little bit during the breaks. What I would like to do is provide in five minutes not an industry opinion, but a perspective on what's gone on actually in the last four meetings.

I think that the overall goal here is a little different from what's stated in the law. It's been there in the air in all the meetings. The goals are early access to new agents, to accelerating the process of drug development for new agents, and, finally -- and this is the industry perspective -- in trying to get some consistency in that process.

Now I think there are three things that have to be taken into account that have come out at these meetings. One is that pediatric rule and exclusivity, although we have tried to divide them for these meetings, I'm a "lumper" and that's why I like these meetings, because the rule lumps adult and pediatric cancers together. I think the Pediatric Rule and exclusivity have to be considered in toto as

moving toward that goal, much in the same way as the Bill of Rights, the Civil Rights Act, and Voting Rights act are not standing alone doing what they are supposed to do.

So I think that as the Agency moves forward, our advice, my advice is that we consider these things working in concert, and that's where Peter established a gap, but I think, again, that pediatric exclusivity and the way these guidances are written around pediatric rule can help to fill that gap.

Second, and I agree with Peter and I think it's the major issue that we face in pediatric drug development in cancer, is that the patient-to-agent ratio is going down, not going up, because I think Pediatric Rule and pediatric exclusivity have been effective. There is anticipatory action being taken by a number of companies. Here I will speak about my company where there's a Vice President for Pediatric Drug Development and a whole Pediatric Drug Development Group.

But we are dealing with small populations,

and Rick Pazdur alluded to this. Where the Pediatric Rule is applied, it's always going to be applied in small adult populations and small pediatric populations because those cancers, with very few exceptions that are linked in the Pediatric Rule specifications, are small tumor burdens, public health burdens.

So we need to link, but we need to link for the sake of the adults who have AML and for the sake of the children who have AML. I think there are two ways to link. They have come out at these meetings. One is sequential development, and I think there are advantages to that. What needs to be stated, I think, in the guidances are what allowances will be made for prior probabilities, not necessarily using a Bayesian approach or a classical approach, but what allowances will be made in the development process for prior knowledge. I think to the extent that those can be specified clearly, they will encourage further anticipatory development without invocation of the rule.

Second is there's parallel development,

and a lot of people, I think, on the academic side and in COG would like to see us do parallel development. In parallel development you'll get faster development, too, but then you need allowances for combining data in studies run in parallel or linking the studies themselves. Here I think the COG and the NCI come into play more than the Agency.

That brings to one of the other points, which is that, in setting priorities, we have to have COG, NCI, CTAP, the Agency, and industry at the same table. Now the industry people can't be at the same table at the same time because there are intellectual property issues. But I think that there has to be some sense in the guidances that provides a fair and consistent way to combine all four of those forces to be able to set priorities, because that's the only way we're going to deal with this patient/agent ratio being very low.

So, with regard to specific invocation of the rule, and this is the final set of points, I think that the guidances should set out, or the letters, or at the meetings, that go out after the meetings, what

bridging studies are required, what specific bridging studies will be acceptable, to the extent that the Agency can do that within the law, and, finally, what will be a significant treatment advance is going to be a very important point in setting priorities.

To the extent possible, if the guidance that comes out of these meetings can set out what is significant treatment advance, I think that that will help, again, determine how much anticipatory activity there will be on the part of the industry drug developers.

So, in summary, again, I think the rule and exclusivity are working. So I think to the extent that these guidances build on that, they are going to be very important. I think that the major issue from both the company's standpoint and I think from COG and every other standpoint is that patient numbers are limited, and we have to have specific guidances that will combine the forces of NCI, COG, industry, interested members, and the Agency, to set priorities in a way that makes sense and that is consistent and fair to both industry and to patients.

CHAIRMAN SANTANA: Thank you for those comments, Wayne. As you note, there is that effort underway. There is a group that meets at COG that has representatives from FDA and industry that tries to address some of these issues. I think there's still a lot more work to be done.

DR. RACKOFF: One more point that came up, if you don't mind, real quickly: There is work going on, too, on this issue of material transfer for pre-clinical studies. It is going to take some time and it is going to take some battles among lawyers sitting down in a room, locking them up, to come up with what might be a master agreement that's acceptable, but under Malcom's guidance that effort is underway.

CHAIRMAN SANTANA: I want to thank you for those comments, Wayne.

Dr. Hirschfeld?

DR. HIRSCHFELD: I also want to thank Dr. Rackoff for his participation previously as an observer and now at the table with us. We hope that we can continue to have industry representatives on the table for this Committee forever essentially.

We will also, I think, have to acknowledge that, of the products that are available to treat patients with cancer, whether they are children or adults, it's been the pharmaceutical industry that has done the brunt of development work and has taken the risks and the distributions and maintained the quality control, and I think should be acknowledge for the contributions that are made in that regard to the public health.

I wanted to pick up on the theme of the matrix because we all feel we are part of a matrix. We should in no sense be perceived as adversarial or that one has a barrier to overcome, or if we can only get around the regulatory hurdles, but rather that we view the regulatory mechanism as a way to ensure high-quality products for patients, ethical and consistent scientific development.

We have been working ourselves with international colleagues, and I think both the pharmaceutical industry and the regulatory community have started on a path which I hope there's no return from. That is to get greater international

cooperation, and it is through international cooperation I think that we can address some of these issues of limitations of numbers and prioritization. I am very heartened that we have at this meeting some international representation and that we look for further development in this arena as well.

CHAIRMAN SANTANA: I want to echo that. I think it has to be a conversation that includes many different parties. I was encouraged to see that there were colleagues from across the ocean who came today and provided some of their effort and time at this meeting. So I want to personally and publicly thank you for that effort.

DR. PAZDUR: But I think it's important that we realize that drug development, in essence, is an international, global development process that occurs. So we don't approve drugs in the United States in isolation. In fact, our regulatory actions have great implications not only in Europe, but throughout South America and Asia.

CHAIRMAN SANTANA: That is correct.

DR. PAZDUR: Just to echo Steve's words,

it is basically we have to be cognizant of our more widespread regulatory activities.

Nevertheless, getting back to this idea of how do we prioritize drugs, I think this is one of the things that we will be using this group as in future areas, to give us the scientific information both using the Pediatric ODAC Subcommittee as well as individual members, in consultation with us on individual applications.

There obviously are many drugs. Which ones to study in pediatrics needs to be really addressed by the people that are studying them and treating the patients. Not all drugs are appropriate, obviously, to be studied in a pediatric population, and we need to have that conversation with you on a long-term basis.

CHAIRMAN SANTANA: And we look forward to providing whatever help and guidance we can to the Agency in that regard.

If there are no further comments, I want to thank -- I'm sorry. I'm sorry, go ahead, Susan.

DR. WEINER: I thought that today's

meeting was really a very good one, Steve, and I thought that the discussion was authentic. I very much appreciate the notion of the matrix, that is, of all participants, since we have an important charge.

But I guess what I would like to add is that I think that at every step of the way we have to be cognizant, every component of this matrix has to be cognizant of how to cut corners, how to make the process more efficient, where things can be more consistent, and how to promote appropriate uniformity. There are certain variables in this process which we can control -- sample sizes, ethics, et cetera. Where we can control it, I think it's really an obligation to the kids and families. Thank you.

CHAIRMAN SANTANA: Thank you, Susan.

I think we have fulfilled our goals as best we could, Dr. Hirschfeld and Dr. Puzdur. So, with no further comment, I want to thank everybody and declare this meeting closed. Thank you.

DR. HIRSCHFELD: Thank you.

(Whereupon, the proceedings concluded at 4:50 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: MEETING

Before: FOOD AND DRUG ADMINISTRATION
ONCOLOGIC DRUGS ADVISORY COMMITTEE
PEDIATRIC SUBCOMMITTEE

Date: WEDNESDAY, NOVEMBER 28, 2001

Place: GAITHERSBURG HOLIDAY INN
TWO MONTGOMERY VILLAGE AVENUE
GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis

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UNIQUE WORDS: **4,029**
TOTAL OCCURANCES: **20,762**
NOISE WORDS: **385**
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